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CLINICAL RESEARCH

Allogeneic Hematopoietic Stem Cell Transplant for Adults over 40 Years Old with Acquired Aplastic Anemia

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Although younger age is associated with favorable prognosis in adults undergoing allogeneic hematopoietic stem cell transplantation (allo-HSCT) for aplastic anemia (AA), other pretransplantation factors may be more important than age. We retrospectively analyzed the impact of older age on transplantation outcomes and survival in a total of 225 adult patients with AA who underwent allo-HSCT: 57 patients >40 years old (older patient group [OPG]) and 168 patients ≤40 years old (younger patient group [YPG]). Age at allo-HSCT ≤40 years, time from diagnosis to allo-HSCT ≤6 months, and matched related donor (MRD) were favorable prognostic factors in all study patients. Risk analysis of survival in the OPG showed that age >50 years was the only poor prognostic factor. Survival did not differ significantly between the YPG and patients <50 years old in the OPG. In conclusion, patients between the ages of 41 and 50 years with severe AA and MRDs should undergo allo-HSCT as early as possible to optimize survival.

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INTRODUCTION

Younger age is associated with favorable prognosis for adults undergoing allogeneic hematopoietic stem cell transplantation (allo-HSCT) for severe aplastic anemia (AA). Most guidelines recommend that only patients <40 years old with suitable HLA-identical sibling donors undergo allo-HSCT because of poor survival after allo-HSCT in older patients [1-3]. Advances in supportive care and transplantation outcomes after allo-HSCT, both from matched unrelated donors (MUDs) and HLA-identical sibling donors, have resulted in better survival outcomes after early transplantation [4]. Therefore, delaying allo-HSCT in older patients after immunosuppressive therapy (IST) failure can result in poor survival. Patients age >30 years receiving a fludarabine-based preparative regimen showed statistically significant improvements in survival outcomes after HLA-identical sibling allo-HSCT [5]. In addition, survival after allo-HSCT from MUDs has improved in recent years [4]. These findings have suggested that early allo-HSCT may be beneficial, even in older patients.

Older patients previously thought unsuitable for allo-HSCT are now undergoing allo-HSCT after reduced intensity conditioning regimens and improved supportive care. Patients 40 to 50 and even 50 to 60 years old with good performance status who failed IST can now be considered for allo-HSCT from MUDs [2,3]. However, the results of allo-HSCT in older patients with severe AA and factors associated with poor survival in these patients have not been fully determined. We, therefore, retrospectively analyzed the impact of age on the survival and transplantation outcomes in adults undergoing allo-HSCT for AA.

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We also assessed risk factors for poor survival among patients >40 years old.

PATIENTS AND METHODS

Patient Eligibility

Patients diagnosed with severe acquired aplastic anemia (SAAA), who were >15 years old at the time of allo-HSCT and had undergone allo-HSCT from a matched related donor (MRD) or alternative donor (AD), regardless of IST history, were eligible. All eligible patients were fully informed of the nature and purpose of this study, and all provided written informed consent before enrollment. All patients fully understood that they were entitled to exit the study without any negative consequences. Exclusion criteria included the presence of congenital aplasia, including Fanconi anemia, Diamond-Blackfan syndrome, or congenital dyskeratosis; or hypoplastic myelodysplastic syndrome. Data were collected from patients with pure red cell aplasia and paroxysmal nocturnal hemoglobinuria during the protocol design phase, but such patients were not included in the final analyses. Patients were divided into 2 groups by age at allo-HSCT, with the younger patient group (YPG) being ≤40 years and the older patient group (OPG) being >40 years old.

Data Collection

The protocol for this retrospective multicenter study was submitted to and approved by the Korean Society of Blood and Marrow Transplantation Clinical Study Committee (approval no. KSBMT07-02) and by the institutional review board of each participating institution. Case report form questionnaires defining items to be evaluated were provided to institutional investigators. If case report form questionnaires were insufficient or incomplete, principal investigators queried institutional collaborators to obtain the missing information. Data collection started in 2007 for 6 months, with 1 institution adding data from 2009.

Evaluation Criteria

The principal outcome of this study was survival after allo-HSCT in the OPG and YPG. The hematological response to IST was assessed during the first 6 months after treatment. Responses to IST were required to be sustained without transfusion, or by administration of growth factors, and were confirmed using a minimum of 2 observations at least 4 weeks apart. A complete response was defined as transfusion-independence plus all cell lines tested being normal for age and gender (SAAA criteria). A partial response (PR) was defined as transfusion-independence but the SAAA criteria had not been met. A nonresponse was defined as transfusion-dependence or when the peripheral blood count criteria for PR had not been attained. Relapse after IST was defined as a decrease in any peripheral blood cell count to <50% of the median sustained count observed during the response phase, or as dependence on transfusion.

ABO blood type incompatibility between donors and recipients was classified as major (ie, the recipient had anti-A and/or anti-B Abs capable of reacting with antigens on donor red cells), minor (ie, the donor had anti-A and/or anti-B Abs capable of reacting with antigens on recipient red cells and tissues), mixed (ie, a transplantation involving a group B donor and a group A recipient, or vice versa), or compatible. Neutrophil engraftment was defined as the first of 3 consecutive days on which recipient absolute neutrophil count (ANC) was $>0.5 \times 10^9$/L after a nadir, and platelet engraftment was defined as the first of 7 consecutive days on which the unsupported platelet count was $>20 \times 10^9$/L. Primary graft failure (or early rejection) was defined as a peripheral ANC $<0.5 \times 10^9$/L persisting for more than 21 days after allo-HSCT. Secondary graft failure was defined as marrow hypoplasia after engraftment, with a requirement for frequent (more than once weekly) platelet transfusion, or an ANC $<0.5 \times 10^9$/L, but without growth factor requirements extending beyond day 60.

Acute and chronic graft-versus-host disease (aGVHD and cGVHD) were diagnosed and graded according to the Seattle criteria [6,7], and sinusoidal obstruction syndrome (SOS) was diagnosed using McDonald's guidelines [8]. Performance status was graded by Eastern Cooperative Oncology Group (ECOG) performance scoring. Relapse was defined as reacquisition of transfusion-dependence or fulfillment of severe/very severe criteria after full engraftment.

Definitions of Survival Times

The starting point for determination of survival parameters was the first day of stem cell infusion. Relapse-free survival, measured only in patients showing successful engraftment and not requiring regular transfusions, was defined as the time from commencement of a conditioning regimen to the date on which the patient was first recorded with disease relapse, or the date of death. Patients without relapse or death were censored at the date of last follow-up. Time to relapse was measured from the day of stem cell infusion to the date on which a patient withdrew from the study because of adverse events, progressive disease, insufficient therapeutic response, death, failure to return for follow-up, refusal of treatment, refusal to cooperate, or withdrawal of consent. If none of these events occurred, patients were censored on the date of last follow-up. Overall survival was measured from the time of commencement of a conditioning regimen to

the date of death, or the last date on which the patient was known to be alive (this constituted censoring).

Statistical Analysis

All analyses were performed on an intention-to-treat basis. The chi-squared test was used to compare categorical variables, and the *t* test was used to compare continuous variables between any 2 groups. Times to engraftment, aGVHD, and cGVHD were estimated using the cumulative incidence function, and differences were compared using Gray's test [9]. Survival curves were computed according to the Kaplan-Meier method, and differences in survival were compared by the log-rank test. A Cox proportional hazards model was used to determine the effects on survival of various prognostic factors, including age, donor/recipient gender matching, number of cells transfused, use of irradiated blood products, time from diagnosis to allo-HSCT, stem cell source, dose of irradiation, HLA matching, method of immune suppression used to prevent GVHD, prior IST, and use of antithymocyte globulin (ATG). All variables were dichotomized and converted into categorical classes. Variables considered in multivariate analysis included patient age and all prognostic factors with P values $<$ .10 in univariate analysis. Differences were assessed using a 2-sided test at the $P = .05$ level of significance. We used the R package (cmprsk) to analyze cumulative incidence, and SPSS version 17 (SPSS, Inc., Chicago, IL) for all other statistical analyses.

RESULTS

Patients

Our initial patient population consisted of 234 consecutive patients with AA who underwent allo-HSCT between 1995 and 2008 at 15 of the 40 transplantation centers in Korea, including most major centers. After excluding 1 patient with pure red cell aplasia and 8 with paroxysmal nocturnal hemoglobinuria, our patient population consisted of 225 adults with AA who underwent allo-HSCT. Median follow-up time for survivors was 36.0 months (range, 1.41-125.72 months). Of these patients, 117 were men (52.0%) and their median age at the time of allo-HSCT was 31.2 years (range, 15-63 years). We determined that 103 patients (45.8%) had received prior IST, including 66 (29.3%) who were treated with ATG or antilymphocyte globulin (ALG); of the latter, only 17 (16.5%) responded, with complete response evident in 2 and PR in 15. ABO blood-type matching was compatible in 110 (53.7%) donor–recipient pairs. Stem cell sources included bone marrow (BM) only in 172 patients (76.4%), peripheral blood only in 46 patients (20.4%), and both in 7 patients (3.1%); 185 pairs (82.2%) were fully HLA-matched. Of the 225 donors, 162 (72.0%) were related and 63 (28.0%) were unrelated; 152 (67.6%) donors were MRDs and 73 (32.4%) were ADs. Classical cyclophosphamide (200 mg/kg)-ATG/ALG (Cy-ATG/ALG) was the most common conditioning regimen used in 126 patients (56.0%). Other conditioning regimens included fludarabine-based regimen (n = 70; 31.1%) and total body irradiation (TBI)-based regimen (n = 24; 10.7%). Drugs used for GVHD prophylaxis were cyclosporine (93.8%), methotrexate (68.0%), prednisolone (7.1%), tacrolimus (5.3%), and mycophenolate mofetil (1.8%).

The YPG and OPG consisted of 168 and 57 patients, respectively, with median ages of 25 years (range, 20-39.9 years) and 45.7 years (range, 40.1-63.6 years), respectively. Gender distribution (P = .614), prior IST (P = .854), packed red cell (PRC) transfusion (P = .671), allo-HSCT from MSD (P = .386), HLA full matching (P = .241), compatible ABO blood-typing (P = .592), classical Cy-ATG (P = .643), TBI as a conditioning regimen (P = .410), ATG/ALG as a conditioning regimen (P = .275), BM as a stem cell source (P = .377), amount of red cell transfusion before allo-HSCT (P = .671), and infused CD34+ cells (P = .473) were all comparable in the 2 groups (Table 1). Amounts of platelet transfusion before allo-HSCT (P = .036), and female donor-to-male recipient transplantation (P = .089) tended to be more frequent in the OPG.

Prognostic Factors Affecting Overall Survival in All Patients

Univariate analysis of all 225 recipients showed that no prior IST (P = .005), age ≤40 years at allo-HSCT (P = .007), time from diagnosis to allo-HSCT ≤6 months (P = .008), sibling donor (P = .002), and HLA full match (P = .019) were significant favorable predictors of overall survival, with ABO compatibility (P = .055) and prior platelet concentrate (PC) transfusion amount (P = .063) being marginally significant (Table 2). In contrast, gender (P = .640), female donor-to-male recipient (P = .499), ECOG performance status at allo-HSCT (P = .948), prior PRC transfusion amount (P = .396), TBI conditioning (P = .525), ATG/ALG conditioning (P = .628), Cy-ATG/ALG conditioning (P = .585), BM as a stem cell source (P = .224), and infused CD34 cells (P = .305) were not significant.

In multivariate analysis, only age ≤40 years at allo-HSCT (hazard ratio [HR] = 0.403; 95% confidence interval [CI] = 0.227-0.715; P = .002), time from diagnosis to allo-HSCT ≤6 months (HR = 0.464; 95% CI = 0.247-0.872; P = .017), and sibling donor (HR = 0.524; 95% CI = 0.294-0.933; P = .028) were favorable prognostic factors (Table 3).

Table 1. Characteristics of Patients

Characteristics	YPG (≤40 years)	OPG (>40 years)	*P* value
Gender, male/female, n (%)	88 (52.4)/80 (47.6)	29 (50.9)/28 (49.1)	.844
Prior IST	78 (46.4)	31 (56.4)	.737
Allo-HSCT from MRD	112 (66.7)	43 (78.2)	.625
HLA full match	136 (81.0)	49 (86.0)	.392
Female-to-male allo-HSCT	25 (14.9)	14 (24.6)	.095
Compatible ABO blood-typing	81 (48.2)	29 (50.9)	.728
Classical Cy (200 mg/kg)-ATG conditioning	96 (57.1)	30 (52.6)	.643
Fludarabine as a conditioning regimen	48 (28.6)	22 (38.6)	.186
TBI as a conditioning regimen	17 (10.1)	7 (12.5)	.648
ATG/ALG as a conditioning regimen	132 (78.6)	41 (71.9)	.304
BM as a stem cell source	137 (81.5)	42 (73.7)	.203
	Median (range)		
Age, yr	27 (15-39.5)	45.7 (40.1-63.6)	<.001
Units of PRC transfusion	12 (0-114)	12 (3-79)	.451
Units of PC transfusion	86 (0-812)	96 (8-574)	.036
Infused CD34+ cells, $\times 10^6$/kg	3.8 (0.11-28)	3.9 (0.2-30.2)	.415

YPG indicates younger patient group; OPG, older patient group; IST, immune suppression therapy; allo-HSCT, allogeneic hematopoietic stem cell transplantation; MRD, matched related donor; Cy, cyclophosphamide; ATG, antithymocyte globulin; TBI, total body irradiation; ALG, antilymphocyte globulin; BM, bone marrow; PRC, packed red cell; PC, platelet concentrate.

Comparative Transplantation Outcomes in the YPG and OPG

Most transplantation outcomes were comparable in the YPG and OPG (Table 4), including rates of engraftment failure ($P = .972$), SOS ($P = .582$), aGVHD ($P = .670$), cGVHD ($P = .828$), secondary graft failure after HSCT ($P = .756$), and time to platelet engraftment ($P = .770$; Figure 1A). However, time to neutrophil engraftment was significantly faster in the OPG ($P = .009$; Figure 1B). Causes of death were similar in the 2 groups ($P = .593$). The most common cause of death was infection (51.3% in the YPG and 54.5% in the OPG; Table 4), followed by GVHD. Death from engraftment failure was more frequent in the YPG (15.4%) than in the OPG (4.5%).

Factors Prognostic for Survival in the OPG

Univariate analysis showed that age at allo-HSCT 40 to 50 versus >50 years (5 year survival rate [5YSR], 76.6% versus 55.9%; $P = .007$), and HLA full matching versus mismatch (5YSR, 60.0% versus 22.5%; $P = .023$) were significantly prognostic for survival in the OPG (Table 5). On multivariate analysis, however, age ≤50 years (HR = 0.307; 95% CI = 0.126-0.748; $P = .009$) was the only favorable factor for overall survival. Prior IST (HR = 0.664; 95% CI = 0.269-1.642; $P = .376$), time from diagnosis to allo-HSCT (HR = 0.563; 95% CI = 0.208-1.521; $P = .257$), and HLA full matching (HR = 0.472; 95% CI = 0.156-1.426; $P = .183$) were not significant.

Overall Survival

Overall survival was significantly longer in the YPG than in the OPG (5YSR, 75.0% versus 55.9%; $P = .007$; Figure 2A). Moreover, overall survival was significantly longer for patients age 40 to 50 years than in those age >50 years (5YSR, 67.9% versus 0%; $P = .016$; Figure 2B). For patients >50 years

Table 2. Univariate Analysis on Survival

Factor	No. of patients	5-year survival rate (%)	*P* value
Female versus male	117 versus 108	74.0 versus 67.7	.640
No prior IST versus prior IST	122 versus 103	77.4 versus 61.9	.005
Age at allo-HSCT ≤40 yr versus >40 yr	168 versus 57	76.6 versus 55.9	.007
Time from Dx to allo-HSCT ≤6 mo versus >6 mo	107 versus 118	78.7 versus 62.8	.008
Sibling donor versus others	162 versus 63	75.6 versus 56.2	.002
ABO compatible versus incompatible	95 versus 110	75.9 versus 59.3	.055
HLA full match versus mismatch	185 versus 40	73.1 versus 55.9	.019
Others versus female donor-to-male recipient	186 versus 39	71.8 versus 63.1	.499
ECOG performance status at allo-HSCT; >1 versus ≤1	33 versus 192	71.8 versus 70.0	.948
Prior PRC transfusion ≤12 units versus >12 units	160 versus 65	71.9 versus 65.9	.396
Prior PC transfusion ≤86 units versus >86 units	149 versus 76	75.3 versus 58.7	.063
Conditioning without versus with TBI	24 versus 201	70.9 versus 65.0	.525
Conditioning with versus without ATG/ALG	173 versus 52	71.6 versus 65.5	.628
Cy-ATG/ALG conditioning versus other	170 versus 55	71.6 versus 65.6	.585
BM as a stem cell source versus others	179 versus 46	72.9 versus 51.6	.224
Infused CD34 infusion >3 versus ≤3 ($\times 10^6$/kg)	144 versus 81	73.3 versus 65.6	.305

IST indicates immune suppression therapy; allo-HSCT, allogeneic hematopoietic stem cell transplantation; Dx, diagnosis; ECOG, Eastern Cooperative Oncology Group; PRC, packed red cell; PC, platelet concentrate; TBI, total body irradiation; ATG, antithymocyte globulin; ALG, antilymphocyte globulin; Cy, cyclophosphamide; BM, bone marrow.

Table 3. Multivariate Analysis on Survival

Factor	HR	95% CI	*P* value
No prior IST versus prior IST	0.786	0.401-1.539	.482
Age at allo-HSCT ≤40 yr versus >40 yr	0.403	0.227-0.715	.002
Time from Dx to allo-HSCT ≤6 mo versus >6 mo	0.464	0.247-0.872	.017
Sibling donor versus others	0.524	0.294-0.933	.028
ABO compatible versus incompatible	0.684	0.392-1.194	.182
HLA full match versus mismatch	0.748	0.353-1.587	.450
Prior PC transfusion ≤86 units versus >86 units	0.676	0.382-1.194	.177

HR indicates hazard ratio; CI, confidence interval; IST, immune suppression therapy; allo-HSCT, allogeneic hematopoietic stem cell transplantation; Dx, diagnosis; PC, platelet concentrate.

old at the time of allo-HSCT, the median survival was 4.3 months (95% CI, 0.0-29.9 months). Overall survival, however, was similar in YPG patients and those in the OPG who were <50 years old (5YSR, 75.0% versus 67.9%; $P = .282$; Figure 3A), in patients in these groups who underwent transplantation from MRDs (5YSR, 82.5% versus 70.7%; $P = .115$; Figure 3B), and in patients who underwent early transplantation (<6 months from diagnosis to transplantation; 5YSR, 84.8% versus 79.1%; $P = .361$; Figure 3C). Overall survival was also similar in YPG patients and those in the OPG who were <50 years old from AD (5YSR, 60.1% versus 55.6%; $P = .835$), and in patients who underwent late transplantation (≥6 months from diagnosis to transplantation; 5YSR, 67.1% versus 70.6%; $P = .361$).

In the OPG, the 5YSR was higher after transplantation from MRD than from AD, but the difference was not statistically significant (60.1% versus 45.2%; $P = .165$). When we compared overall survival in YPG patients who underwent allo-HSCT >6 months from diagnosis with that in OPG patients who underwent allo-HSCT ≤6 months from diagnosis, we found that 5YSR were almost similar (67.1% versus 62.2%; $P = .905$; Figure 4A). Moreover, survival rates were similar in YPG patients who underwent allo-HSCT from an AD and OPG patients who underwent allo-HSCT from a sibling donor (60.1% versus 60.1%; $P = .723$; Figure 4B).

DISCUSSION

Patients <40 years old with an HLA-identical sibling donor should undergo allo-HSCT before IST, whereas allo-HSCT from MUDs in older patients can be attempted after IST failure. It is unclear, however, whether allo-HSCT should be delayed in patients age >40 years with suitable HLA-identical sibling donors, especially because early transplantation has been associated with better survival outcomes after allo-HSCT in patients with AA [4,10].

Older age has shown negative impacts on platelet recovery, incidence of GVHD, and mortality after allo-HSCT [11]. More recently, however, allo-HSCT outcomes have improved, although IST outcomes have not [1,12]. Our univariate analyses showed that factors significantly associated with patient survival included no prior IST ($P = .005$), age

Table 4. Transplantation Outcomes between YPG versus OPG

Characteristics	YPG (≤40 years)	OPG (>40 years)	*P* value
Engraftment failure, n (%)			
Any	35 (20.8)	12 (21.1)	.972
Neutrophil	16 (9.5)	4 (7.0)	.566
Platelet	23 (13.7)	11 (19.3)	.307
SOS, n (%)	13 (7.7)	6 (10.5)	.582
aGVHD, n (%)	40 (23.8)	12 (21.1)	.670
cGVHD, n (%)	36 (21.4)	13 (22.8)	.828
Extensive cGVHD, n (%)	15 (8.9)	4 (7.0)	.788
Secondary graft failure after HSCT, n (%)	10 (6.0)	4 (7.0)	.756
Causes of death	n = 39	n = 22	.593
Infection, n (%)	20 (51.3)	12 (54.5)	
GVHD, n (%)	7 (17.9)	4 (18.2)	
Engraftment failure, n (%)	6 (15.4)	1 (4.5)	
Hemorrhage	2 (5.1)	2 (9.1)	
	Cumulative incidents, median (range)		
Time to ANC >500/μL, d	17 (8-32)	16 (9-23)	.009*
Time to platelet >20K/μL, d	21 (5-423)	19 (10-122)	.770*
Time to aGVHD, d	30.5 (0-165)	22.5 (8-108)	.726*
Time to cGVHD, mo	4.4 (2.2-23.7)	4.8 (2-12)	.483*

YPG indicates younger patients group; OPG, older patients group; SOS, sinusoidal obstruction syndrome; aGVHD, acute graft-versus-host disease; cGVHD, chronic graft-versus-host disease; HSCT, hematopoietic stem cell transplantation; ANC, absolute neutrophil count.
*Calculated by Gray test.

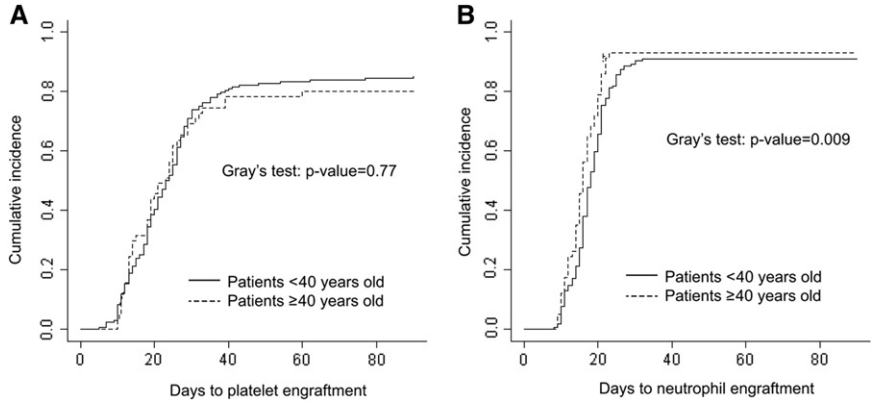

Figure 1. Cumulative incidence of platelet (A) and neutrophil engraftment (B).

≤40 years at allo-HSCT ($P = .007$), time from diagnosis to allo-HSCT ≤6 months ($P = .008$), sibling donor ($P = .002$), and HLA full match ($P = .019$). Multivariate analysis, however, showed that only age ≤40 years at allo-HSCT ($P = .002$), time from diagnosis to allo-HSCT ≤6 months ($P = .017$), and sibling donor ($P = .028$) were favorable prognostic factors, confirming that age >40 years was significantly associated with poor survival outcomes, but also showing that delayed allo-HSCT was an unfavorable risk factor. When we analyzed outcomes in our OPG, however, we found that age >50 years was associated with poor prognosis, whereas age 40 to 50 years was associated with a more favorable outcome after early allo-HSCT.

Compared with the YPG, patients in the OPG did not have significantly poorer transplantation outcomes, including engraftment failure ($P = .848$), SOS ($P = .591$), aGVHD ($P = .445$), cGvHD ($P = .105$), secondary graft failure after HSCT ($P = .754$), and time to platelet engraftment ($P = .770$). Moreover, time to neutrophil engraftment was faster in the OPG ($P = .009$), suggesting that allo-HSCT can be performed in older patients without additional risks of poorer transplantation outcomes. A previous study, however, found that GVHD was significantly more frequent in older than in younger patients [11].

Age was less significant in patients under 50 years old, with 5YSRs similar in the YPG and in patients <50 years in the OPG (75.0% versus 67.9%; $P = .282$). Moreover, these 2 patient cohorts had similar 5YSRs after transplantation from MRDs (82.5% versus 70.7%; $P = .115$) and after early transplantation <6 months after diagnosis (84.8% versus 79.1%; $P = .361$). These findings suggest that allo-HSCT can be performed successfully in patients between 40 and 50 years of age.

Our findings on 43 patients >40 years old who underwent allo-HSCT from MRDs can be compared with those of a study reporting the outcomes of allo-HSCT from MRDs for SAA in 23 patients >40 years of age [13]. Median age (45.8 versus 49 years), male sex (60% versus 52.2%), donor–recipient sex mismatch

Table 5. Prognostic Factors on Survival in Patients >40 years old

Factor	No. of patients	Univariate analysis		Multivariate analysis		
		5YSR (%)	*P* value	HR	95% CI	*P* value
Female versus male	29 versus 28	51.4 versus 59.8	.469	—	—	—
No prior IST versus prior IST	32 versus 25	62.0 versus 47.2	.123	0.664	0.269-1.642	.376
Age at allo-HSCT >40 and ≤50 yr versus >50 yr	41 versus 16	76.6 versus 55.9	.007	0.307	0.126-0.748	.009
Time from Dx to allo-HSCT ≤6 mo versus >6 mo	30 versus 27	62.2 versus 48.3	.129	0.563	0.208-1.521	.257
Sibling donor versus others	43 versus 14	58.5 versus 46.8	.405	—	—	—
ABO compatible versus incompatible	29 versus 28	56.8 versus 54.0	.830	—	—	—
HLA full match versus mismatch	49 versus 8	60.0 versus 22.5	.023	0.472	0.156-1.426	.183
Others versus female donor-to-male recipient	43 versus 14	58.2 versus 49.7	.890	—	—	—
ECOG performance status at allo-HSCT; ≤1 versus >1	46 versus 11	52.1 versus 70.1	.297	—	—	—
Prior PRC transfusion ≤12 units versus >12 units	33 versus 24	56.5 versus 53.3	.957	—	—	—
Prior PC transfusion ≤86 units versus >86 units	28 versus 29	55.2 versus 54.6	.933	—	—	—
Conditioning without versus with TBI	50 versus 7	54.1 versus 66.7	.430	—	—	—
Conditioning with versus without ATG/ALG	41 versus 16	57.4 versus 53.0	.683	—	—	—
Cy-ATG/ALG conditioning versus other	41 versus 16	57.4 versus 53.0	.683	—	—	—
BM as a stem cell source versus others	42 versus 15	61.4 versus 33.4	.950	—	—	—
Infused CD34 infusion >3 versus ≤3 ($\times 10^6$/kg)	34 versus 23	56.2 versus 55.3	.740	—	—	—

5YSR indicates 5-year survival rate; HR, hazard ratio; CI, confidence interval; IST, immune suppression therapy; allo-HSCT, allogeneic hematopoietic stem cell transplantation; Dx, diagnosis; ECOG, Eastern Cooperative Oncology Group; PRC, packed red cell; PC, platelet concentrate; TBI, total body irradiation; ATG, antithymocyte globulin; ALG, antilymphocyte globulin; Cy, cyclophosphamide; BM, bone marrow.

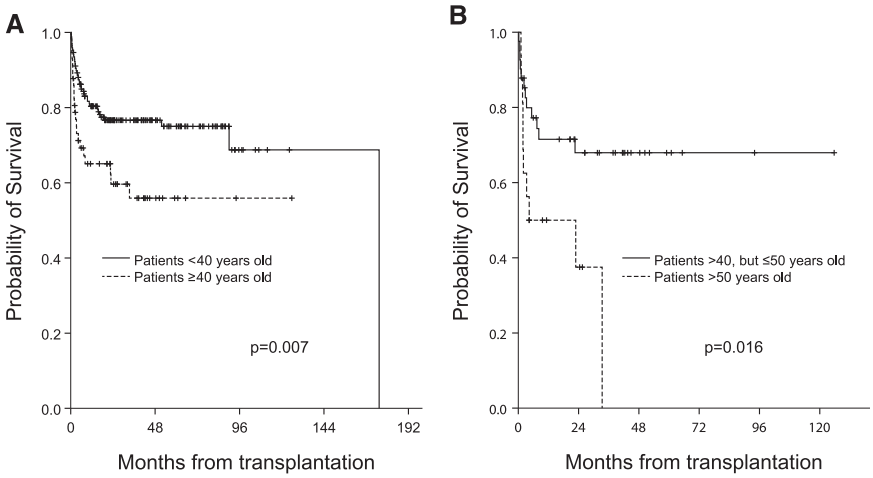

Figure 2. Overall survival. (A) Shows overall survival of all patients comparing patients age <40 years old and >40 years old. (B) Shows overall survival of patients >40 years old comparing patients <50 years old and patients >50 years old.

(52.5% versus 48%), major ABO mismatch (17.9% versus 17%), and median duration of AA before allo-HSCT (3.8 versus 3 months) were comparable, although the frequencies of very severe AA (7.5% versus 65%) and history of pre-allo-HSCT IST (27.5% versus 48%) were lower in our study. The rates of neutrophil engraftment failure (7.5% versus 4.3%), cGVHD (27.5% versus 26%), and overall survival rates (60.1% at 4 years versus 65% at 10 years) were also similar. We found, however, that the median time of neutrophil engraftment was delayed (15 versus 24 days), and the rates of grade II to IV aGVHD (50% versus 84.2%) and death from infection (17.5% versus 35%) were more frequent in the earlier report. When we combined rates of death from infection, engraftment failure (6.3%), and GVHD (18.8%), the overall cause of death would be multiorgan failure and infection, with the actual incidence of death of infection being similar.

Our previous report for small number of unrelated transplantation in patients with AA without TBI showed low cGVHD rates [14]. Also, our recent nationwide data on unrelated transplantation in AA without TBI (not published yet) showed similar results. However, a Korean unrelated transplantation trial using TBI revealed a high rate of cGVHD [15]. Therefore, we think the low proportion of TBI-conditioning in this data resulted in low incidence of cGVHD, although many unrelated transplantations were included. Our cumulative incidence of GVHD was similar with that of allo-HSCT from unrelated donor in SAA patients from the Japanese Marrow Donor Program [16]. Although there were some differences, these 2 studies reported similar and comparable outcomes with younger patients.

Marsh et al. [17] reported new alemtuzumab with fludarabine and cyclophosphamide conditioning, which enrolled 24% of patients older than 50 years. Factors influencing overall survival were HSCT comorbidity 2-year index (92% with score 0-1 versus 42% with score >2; $P < .001$) and age (92% for age <50 years versus 71% >50 years; $P < .001$). Seattle data showed 65% overall survival in patients over 40 years, and our data showed similar survival between

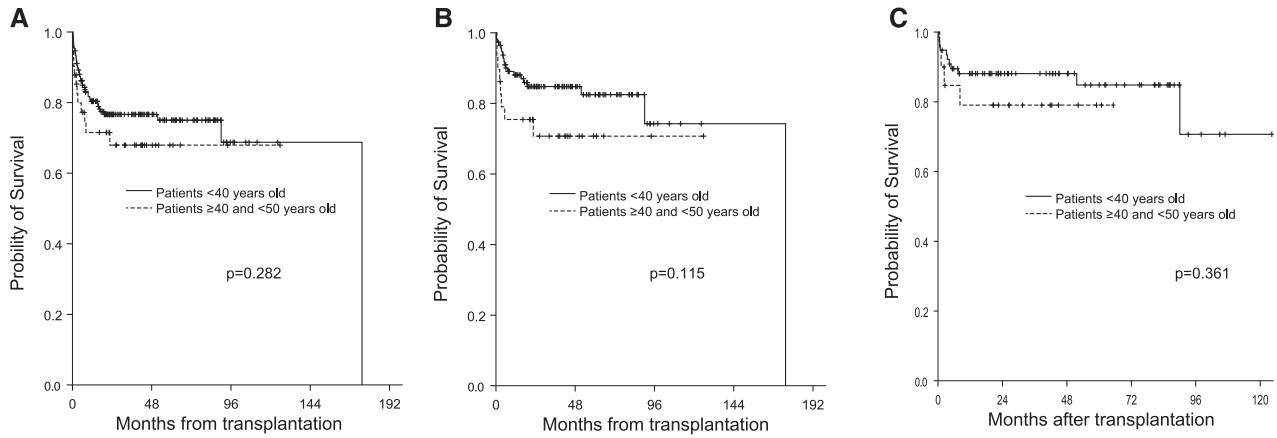

Figure 3. Overall survival in patients <50 years old comparing patients <40 years old and patients >40 years. Overall survival in all patients (A), in transplantation from HLA-identical related donor (B), and in early transplantation (<6 months from diagnosis to transplantation) (C).

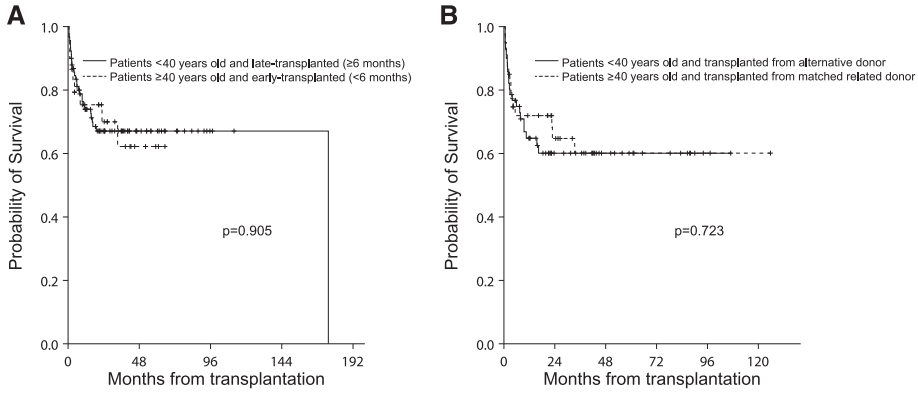

Figure 4. Overall survival comparing unfavorable younger patients and favorable older patients. Overall survival comparing patients who were <40 years old and underwent transplantation from an alternative donor versus patients who were >40 years old and received a transplant from a matched sibling donor (A); comparing patients who were <40 years old and whose time from diagnosis to transplantation was >6 months versus patients who were >40 years old and whose time from diagnosis to transplantation was <6 months (B).

patients <40 years and 40 to 50 years old [13]. All these data suggest that patients >40 years but under 50 years old with an MRD should proceed to allo-HSCT promptly.

The overall survival of patients >40 years old with favorable factors (early transplantation or having MRD) was almost identical to that of patients <40 years old with unfavorable factors (later transplantation or AD). Thus, although age is a very important clinical factor, younger patients with other unfavorable clinical factors may have outcomes similar to older patients, indicating that age is not the only absolute cutoff for performing allo-HSCT in patients with AA.

This study has several limitations, including its retrospective design, the small numbers of patients >40 and >50 years old, and the small numbers who underwent allo-HSCT from ADs, numbers that may have weakened the statistical power of this study. Although we assessed many risk factors, our comparison of transplantation outcomes and survival between the YPG and OPG could not consider all possible clinical conditions.

In conclusion, our findings suggest that older patients with severe AA can safely undergo allo-HSCT. Older patients with MRD should undergo allo-HSCT as early as possible to prolong survival, especially if they are <50 years old.

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